Triazolines. 19.[1] Nickel Peroxide Oxidation of Δ^2-1,2,3-Triazolines. A Versatile General Synthetic Route to 1*H*-1,2,3-Triazoles

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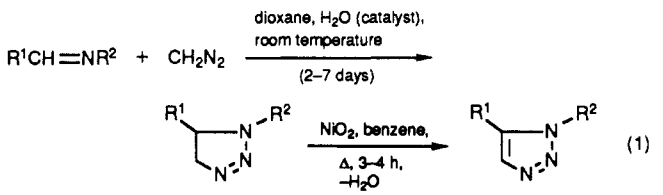
Although the oxidative dehydrogenation of Δ^2-1,2,3-triazolines using potassium permanganate in a phase-transfer catalyzed reaction system affords a convenient route for the synthesis of a number of 1-aryl-5-heteroaryl-substituted 1*H*-1,2,3-triazoles, the reaction has limited scope and fails to yield satisfactory results when electron-withdrawing and/or sterically crowded groups are present on the triazoline molecule. Also, in a few cases, the formation of less than 10% of a high melting side product, identified to be an imine in the case of triazole **3**, makes product purification very tedious. We have now found for the first time that nickel peroxide (NiO_2) functions as a superior oxidizing agent for the triazoline ring system in general. Dehydrogenation occurs exclusively and no side products are observed. Triazolines bearing electron-withdrawing and/or sterically crowded groups are smoothly oxidized to the respective triazoles in good yields. Steric crowding prevents the bulky permanganate ion from closely approaching the reaction site, whereas the effectiveness of NiO_2 oxidation, presumed to occur via hydroxyl radicals, is unaltered. NiO_2 oxidation of 1,5-substituted 1,2,3-triazolines thus provides an efficient general route for the synthesis of a wide variety of both 1,5-diaryl- and 1-aryl-5-heteroaryl-1*H*-1,2,3-triazoles. 1,5-Substituted 1,2,3-triazolines bearing both aryl and heteroaryl groups can be readily prepared by the regiospecific addition of diazomethane in dioxane solution to Schiff bases (imines) in the presence of water as a catalyst. Thus triazoline oxidation may be entered as a primary, major synthetic route for triazole preparation.

During the course of our studies on the anticonvulsant potential of 1,5-substituted 1,2,3-triazolines and the respective triazoles,[3-6] we had found that the oxidative dehydrogenation of triazolines using potassium permanganate in a refluxing benzene–water two-phase system in the presence of a phase-transfer catalyst afforded a convenient route for the synthesis of 1-aryl-5-heteroaryl-substituted 1*H*-1,2,3-triazoles.[4,7,8] However, an investigation of substituent effects on the oxidation revealed that the reaction had limited scope and failed to yield satisfactory results when electron-withdrawing and/or sterically crowded groups were present on the triazoline molecule.[8] Also, in a few cases, the formation of less than 10% of a side product, identified as the methyl pyridyl ketone imine in the case of triazole **3**,[8,9] made purification very tedious, and satisfactory yields of products with sharp melting points were difficult to obtain. Our continued interest to develop triazoline oxidation as a general route to triazole synthesis prompted us to search for a superior oxidizing agent and led us to find for the first time that nickel peroxide (NiO_2) functions as an effective oxidant for the triazoline ring system in general (eq 1).



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Results and Discussion

Selenium dioxide, SeO_2,[10] chromium trioxide supported on graphite, CrO_3–C_6,[11] and elemental sulfur[12] failed because of the susceptibility of the triazoline ring system to acid-induced decomposition.[13,14] Activated manganese dioxide, $Mn(IV)O_2$,[15] and palladium supported on carbon, Pd–C,[16] although successful in the oxidation of the structurally analogous pyrazolines, left triazolines unaffected.[17] Although the potential of NiO_2 as an oxidant in organic synthesis has been recognized for a long time,[18-20] oxazolines and thiazolines are the only hetero-

(1) This paper was presented in part at the Tenth International Congress of Heterocyclic Chemistry, Waterloo, Canada, 1985.
(2) This paper is based on the undergraduate honors paper of S.B.E. submitted to the Independent Problems Course in Chemistry. It won first prize in the 1984–85 Oswald Research and Creativity Competition for undergraduate students at the University of Kentucky.
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(18) Nakagawa, K.; Konaka, R.; Nakata, T. *J. Org. Chem.* **1962**, *27*, 1597. In our laboratories, the NiO_2 cake was broken to small lumps and air-dried for about a week until it could be powdered by grinding in a mortar. Drying over anhydrous calcium chloride in a vacuum desiccator[18] took several days for the slimy preparation to yield a completely dried product. Ordinary household laundry Clorox containing 5.2% sodium hypochlorite served as the oxidizing agent.
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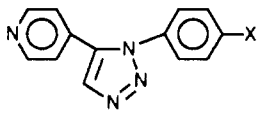
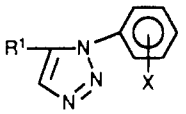
Table I. NiO_2 Oxidation of 1-Aryl-5-(4-pyridyl)-1,2,3-triazolines



compd no.	X	mp (°C)	yield (%)[a] (reflux time, h)[b] NiO_2	yield (%)[a] (reflux time, h)[b] $KMnO_4$ (phase-transfer catalysis)	^1H NMR, δ for ring CH	mol for. or lit. mp (°C)	anal.[c] C, H, N
1	4-CH_3	128–129	51.4 (3) (mp 108–122)		8.02 (s)	128–129[7]	
			45.4	73.0 (2)			
2	4-OCH_3	144–145	76.9 (3) (mp 135–144)		8.07 (s)	143–145[7]	
			53.8	56.0 (5)			
3	4-Cl	124.5–125.5	57.7 (3)	70.0 (3)[d] (mp 110–125)	7.87 (s)	124–126[7]	
4	4-NO_2	182–183	65.5 (3)	44.8 (4) (mp 172–183)	8.15 (s)	$C_{13}H_9N_5O_2$	C, H, N
5	H	105–107	67.0 (3)	65.0 (2)	8.10 (s)	105–107[7]	
6	4-Br	127–129	71.6 (32)		8.05 (s)	$C_{13}H_9N_4Br$	C, H, N
7	4-F	154.9–155.9	77.8 (3)	75.0 (4)	8.06 (s)	155–156[4]	

[a] Yields are for the purified products. [b] The reflux period is shown in parentheses next to yield. [c] The elemental analysis (C, H, N) for all new compounds were well within ±0.4% of the calculated values. [d] For 150 mL of benzene, only 200 mL of water (instead of 300 mL) was used. See note under ref 8.

Table II. NiO_2 Oxidation of 1,5-Substituted 1,2,3-Triazolines Bearing Electron-Withdrawing Substituents



compd no.	R^1	X	mp (°C)	yield (%)[a] (reflux time, h)[b] NiO_2	yield (%)[a] (reflux time, h)[b] $KMnO_4$ (phase-transfer catalysis)	^1H NMR, δ for ring CH	mol for. or lit. mp (°C)	anal.[c] C, H, N
8	2-pyridyl	4-NO_2	163–165	45.5 (3)		8.18 (s)	$C_{13}H_9N_5O_2$	C, H, N
9	4-$NO_2C_6H_4$	H	144–145	59.7 (3)	35.5 (4) (mp 140–144)	8.10 (s)	145[8]	
10	phenyl	4-Br	100–102	79.0 (3)	63.0 (4) (mp 98–102 with previous softening)	7.90 (s)	100–102[4]	
11	2-pyridyl	4-Br	104–105	71 (3)	45 (7) (mp 103–105)	8.09 (s)	103–105[4]	
12	2-pyridyl	3,4-F_2	103–106	61 (4)	46 (4) (mp 101–102.5)	8.08 (s)	101–102.5[4]	
13	4-pyridyl	3,4-Cl_2	138–140	69 (4)	40 (3)	7.99 (s)	138–140[4]	
14	2-quinolyl	4-OCH_3	118–120	60 (3)		8.25 (s)	$C_{18}H_{14}N_4O$	C, H, N

[a] Yields are for the purified products. [b] The reflux period is shown in parentheses next to yield. [c] The elemental analysis (C, H, N) for all new compounds were well within ±0.4% of the calculated values.

cyclic systems that have been investigated with this reagent.[21,22] There are no reports on the use of NiO_2 for the oxidation of 1,2,3-triazolines, except a single isolated case where a triazoline-4-carboxamide was oxidized to the respective triazole in 41% yield.[22]

Presented in Table I are the results of oxidation of a series of 1-aryl-5-(4-pyridyl)-1,2,3-triazolines.[23] Optimum conditions for the triazoline → triazole conversion were determined by using triazoline **3**, 1 equiv requiring 12 equiv of NiO_2 for successful oxidation. Unlike in the permanganate reaction, no side product was observed in the conversion of both triazolines **3** and **10** to the respective triazoles. However, in the NiO_2 oxidation, while electron-donating groups on the 1-phenyl ring showed a tendency to lower triazoline → triazole conversion (compounds **1** and **2**), electron-withdrawing groups facilitated the same, an order that is in reverse of that observed for the permanganate oxidation.[7,8] Commensurate with this trend, NiO_2 was found to be an effective oxidant for triazolines bearing strong electron-withdrawing groups. In the permanganate oxidation of 1,5-diaryltriazolines, electron-withdrawing groups on either or both of the aryl rings, generally, did not facilitate reaction, the effect being more pronounced when they were on the 5-phenyl ring.[8] On the other hand, NiO_2 oxidation proceeded with ease for both aryl- and heteroaryl-substituted triazolines (compounds **10–14**, Table II) and regardless of whether the NO_2 substituent was on the 1 or 5 aryl ring (compounds **8** and **9**, Table II; **4**, Table I). Thus, 1-(*p*-nitrophenyl)-5-(4-pyridyl)-1,2,3-triazoline (**4**), which resisted oxidation in the permanganate procedure, underwent efficient oxidation with NiO_2 to yield 65.5% of the pure triazole. NiO_2 oxidation of 1-phenyl-5-(*p*-nitrophenyl)-1,2,3-triazoline (**9**) to the corresponding triazole in satisfactory yields is quite remarkable; in the permanganate oxidation, the reaction

Scheme I

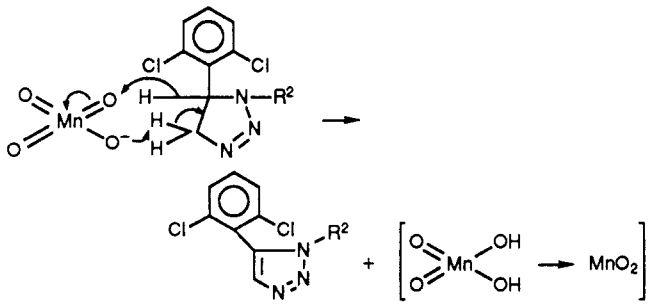


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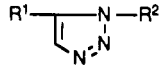
Table III. NiO_2 Oxidation of 1,5-Diaryl-1,2,3-triazolines Bearing Sterically Crowded Ortho-Substituted 5-Phenyl Groups



compd no.	R^1	R^2	mp (°C)	yield (%)[a] (reflux time, h)[b] NiO_2	yield (%)[a] (reflux time, h)[b] $KMnO_4$ (phase-transfer catalysis)	^1H NMR, δ for ring CH	mol. for or lit. mp (°C)	anal.[c] C, H, N
15	2-ClC_6H_4	4-OCH_3Ph	95–97	63 (4)		7.87 (s)	$C_{15}H_{12}N_3OCl$	C, H, N
16	2-ClC_6H_4	3,4-Cl_2Ph	97–99	63 (3)	17 (18)	7.94 (s)	99–100[8]	
17	2,4-$Cl_2C_6H_3$	Ph	90–92	65 (4)		7.88 (s)	$C_{14}H_9N_3Cl_2$	C, H, N
18	2,4-$Cl_2C_6H_3$	4-ClPh	143–145	56 (3)[d]		8.00 (s)	$C_{14}H_8N_3Cl_3$	C, H, N
19	2,4-$Cl_2C_6H_3$	3-ClPh	97–99	56 (4)		7.88 (s)	$C_{14}H_8N_3Cl_3$	C, H, N
20	2,4-$Cl_2C_6H_3$	4-FPh	147–149	52 (4)		7.87 (s)	$C_{14}H_8N_3Cl_2F$	C, H, N
21	2,4-$Cl_2C_6H_3$	4-BrPh	132–134	73 (4)		7.87 (s)	$C_{14}H_8N_3Cl_2Br$	C, H, N
22	2,4-$Cl_2C_6H_3$	4-CF_3Ph	114–116	70 (4)		7.89 (s)	$C_{15}H_8N_3Cl_2F_3$	C, H, N
23	2,4-$Cl_2C_6H_3$	3-CF_3Ph	78.5–80.5	60 (4)		7.90 (s)	$C_{15}H_8N_3Cl_2F_3$	C, H, N
24	2,6-$Cl_2C_6H_3$	Ph	134–136	50 (4)		7.85 (s)	$C_{14}H_9N_3Cl_2$	C, H, N
25	2,6-$Cl_2C_6H_3$	4-ClPh	137–139	63 (4)		7.85 (s)	$C_{14}H_8N_3Cl_3$	C, H, N
26	2,6-$Cl_2C_6H_3$	3-ClPh	103–106	52 (3)	34 (4) (mp 91–98)	7.98 (s)	$C_{14}H_8N_3Cl_3$	C, H, N
27	2,6-$Cl_2C_6H_3$	4-BrPh	152–155	74 (3)	<1 (18)	7.95 (s)	155–158, with previous softening from 150[8]	
28	2,6-$Cl_2C_6H_3$	4-CF_3Ph	129.5–131.5	76 (4)		7.88 (s)	$C_{15}H_8N_3Cl_2F_3$	C, H, N
29	2,6-$Cl_2C_6H_3$	3-CF_3Ph	129–130.5	66 (4)		7.88 (s)	$C_{15}H_8N_3Cl_2F_3$	C, H, N
30	2,4-$Cl_2C_6H_3$	3,4-Cl_2Ph	134–136	69 (4)		7.87 (s)	$C_{14}H_7N_3Cl_4$	C, H, N
31	2-$NO_2C_6H_4$	4-ClPh	138.5–140	75.5 (4)		7.82 (s)	$C_{14}H_9N_4O_2Cl$	C, H, N
32	2-$NO_2C_6H_4$	3,4-Cl_2Ph	125–127	76 (3)		7.81 (s)	$C_{14}H_8N_4O_2Cl_2$	C, H, N
33	2-$NO_2C_6H_4$	3-CF_3Ph	116.5–118	70 (4)		7.85 (s)	$C_{15}H_9N_4O_2F_3$	C, H, N

[a] Yields are for the purified products. [b] The reflux period is shown in parentheses next to yield. [c] The elemental analysis (C, H, N) for all new compounds were well within ±0.4% of the calculated values. [d] When Ni_2O_3 was used as the oxidant, 63% triazole was obtained in this case.

product containing unchanged triazoline could not be crystallized to yield the pure triazole.[8] Permanganate dehydrogenation presumably involves interaction of the C-4 and C-5 positions on the triazoline molecule with two sites on the permanganate ion (Scheme I),[9] analogous to triazoline aromatization, which occurs by loss of a proton from the 4-position and an anion from the 5-position to form a stable molecule for expulsion.[13,24] Apparently, an electron-withdrawing substituent in the 5-position would make hydride abstraction from this position difficult to attain.

NiO_2, unlike permanganate, was found most efficient in the oxidation of those triazolines bearing a sterically crowded ortho-substituted phenyl ring in the 5-position (Table III). Steric crowding apparently prevents the bulky permanganate ion from approaching the triazoline molecule (Scheme I),[9] whereas NiO_2 oxidations presumed to involve free radicals[25-27] are unaffected. The superior efficacy of NiO_2 over the permanganate oxidizing agent in the oxidation of a variety of sterically crowded triazolines is apparent from the results presented in Table III; they are indeed in agreement with what would be expected on the basis of the oxidation mechanisms of the two oxidants. While the permanganate oxidation yielded less than 1% of pure triazole **27** after 18 h of reaction,[8] an outstanding yield of 73.8% was obtained in the NiO_2 oxidation after only a 3-h reaction period. Likewise, NiO_2 oxidation led to yields of 63.0% and 52% respectively for triazoles **16** and **26**; the permanganate oxidation failed to yield a pure product for compound **26** when the oxidation was run for only 4 h, same as that for the NiO_2 reaction. In addition, sterically crowded triazolines bearing electron-withdrawing nitro groups in the ortho position of the 5-phenyl (**31**, **32**, and **33**) afforded equally good yields of the triazoles upon NiO_2 oxidation. NiO_2 oxidation of sterically crowded triazolines thus provides a simple, versatile route for the synthesis of a number of hitherto unknown sterically crowded 1*H*-1,2,3-triazoles.

Nickel peroxide exists as the Ni(II) oxide, NiO_2, or the Ni(III) oxide, Ni_2O_3, although, all of the reported oxidations[18,19,21,22] are conducted with the readily accessible NiO_2.[18] Oxidation of triazolines **2**, **3**, **6**, and **7** utilizing Ni_2O_3 (Aldrich Chemical Company) showed no significant difference in triazole yields except 6 equiv of Ni_2O_3 were sufficient to effect oxidation, perhaps due to the increased "available oxygen" content of Ni_2O_3. However, the laboratory preparation of NiO_2[18] is far more cost effective when several oxidation reactions need to be conducted as we are now doing, routinely synthesizing all of our triazoles by the NiO_2 oxidation of triazolines.

In conclusion, NiO_2 oxidation of 1,5-substituted-1,2,3-triazolines provides a versatile, general route for the synthesis of both 1,5-diaryl- and 1-aryl-5-heteroaryl-substituted 1*H*-1,2,3-triazoles. More importantly, NiO_2 oxidation, unlike the permanganate oxidation procedure, allows for the synthesis, in good yields, of sterically crowded triazoles and triazoles bearing strong electron-withdrawing groups. It is quick and simple and does not entail tedious reaction workup;[7,8] it provides the method of choice for the synthesis of a wide variety of triazoles. The synthetic utility of the 1,3-cycloaddition reactions of azides with acetylenes is greatly limited by their lack of reactivity and regiospecificity.[24] On the other hand, 1,5-substituted 1,2,3-triazolines bearing both aryl and heteroaryl groups can be readily prepared by the regiospecific addition of diazomethane in dioxane solution to Schiff bases (imines) in the presence of water as a catalyst[3,4,28-30] (eq 1). Thus, triazoline oxidation may be entered as a primary, major

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synthetic route for triazole preparation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected. NMR spectra were run on a Varian XL-300 300 MHz spectrometer in $CDCl_3$ solutions with TMS as internal standard. C, H, and N elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Nickel Peroxide (NiO_2) Oxidation of 1,2,3-Triazolines: Synthesis of 1*H*-1,2,3-Triazoles. To a solution of the 1,2,3-triazoline[3-4,23,28-30] (0.005 mol) in reagent-grade benzene (100 mL) was added dried, finely powdered NiO_2[18] (0.060 mol), and the mixtire was refluxed with vigorous magnetic stirring for 3-4 h. The reaction mixture was then allowed to cool to room temperature and filtered under gravity to remove the spent NiO_2. The residual NiO_2 was washed with hot $CHCl_3$, and the combined filtrates were subjected to rotary evaporation. The resulting oily residue was cooled and triturated with petroleum ether or an ether-petroleum ether mixture, when it solidified to a clean crystalline mass, and the colored impurities remained in solution. Many of the triazoles at this point were quite pure, giving reasonably sharp melting points and little, if any, N_2 gas evolution, which is indicative of the presence of appreciable amounts of unreacted triazoline.[28] Recrystallization from acetone-petroleum ether gave analytically pure samples, with only slight changes in the previously determined melting points.

Triazoles **1**, **2**, and **26**, however, showed wide melting point ranges with significant gas evolution; NMR analysis indicated 28% unreacted triazoline **26** and 12-13% **1** and **2**. Two crystallizations from acetone-petroleum ether mixture were required before the characteristic ABC multiplet of the $4CH_2$-5CH triazoline protons[23] in the δ 4-6 region disappeared from the NMR spectrum. Triazole **26**, prepared by permanganate oxidation, resulted in 34% yield, of which almost 30% was unchanged triazoline, as revealed by NMR.

Synthesis of 1,2,3-Triazolines. The 1,2,3-triazolines were synthesized according to the Kadaba procedure by the cycloaddition of diazomethane to Schiff bases in a dioxane-water mixture, utilizing the catalytic effect of water on the addition (eq 1).[3,4,23,28-30] Triazolines **4**, **14**, **20**, **22**, **25**, **28**, **29**, **31**, and **33** were newly synthesized and gave satisfactory elemental analysis for C, H and N; compound numbers, melting points, and percent yields of pure compounds were as follows: **4**, 151-152 dec, 69; **14**, 139-140 dec, 78; **20**, 127-128 dec, 65; **22**, 67-70, 45; **25**, 150-153 dec, 83; **28** 133-136 dec, 48; **29**, 130-132 dec, 80; **31**, 146-148 dec, 70; **33**, 84-88, 73.

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Registry No. **1**, 68090-19-7; **2**, 68090-21-1; **3**, 68090-20-0; **4**, 129239-50-5; **5**, 68090-18-6; **6**, 129239-51-6; **7**, 110684-22-5; **8**, 129239-52-7; **9**, 31802-50-3; **10**, 18250-08-3; **11**, 110684-40-7; **12**, 110684-41-8; **13**, 110684-21-4; **14**, 129239-53-8; **15**, 128229-10-7; **16**, 84817-40-3; **17**, 128229-11-8; **18**, 128229-12-9; **19**, 128229-13-0; **20**, 128252-72-2; **21**, 129239-54-9; **22**, 128229-14-1; **23**, 128229-15-2; **24**, 128229-16-3; **25**, 128229-17-4; **26**, 128229-18-5; **27**, 84817-41-4; **28**, 129239-55-0; **29**, 129239-56-1; **30**, 129239-57-2; **31**, 129239-58-3; **32**, 129239-59-4; **33**, 129239-60-7; NiO_2, 12035-36-8; 1-(4-methylphenyl)-5-(4-pyridyl)-1,2,3-triazoline, 55643-89-5; 1-(4-methoxyphenyl)-5-(4-pyridyl)-1,2,3-triazoline, 55643-90-8; 1-(4-chlorophenyl)-5-(4-pyridyl)-1,2,3-triazoline, 55643-87-3; 1-(4-nitrophenyl)-5-(4-pyridyl)-1,2,3-triazoline, 129239-61-8; 1-phenyl-5-(4-pyridyl)-1,2,3-triazoline, 55643-88-4; 1-(4-fluorophenyl)-5-(4-pyridyl)-1,2,3-triazoline, 97230-32-5; 1-(4-nitrophenyl)-5-(2-pyridyl)-1,2,3-triazoline, 110684-20-3; 1-phenyl-5-(4-nitrophenyl)-1,2,3-triazoline, 10445-18-8; 1-(4-bromophenyl)-5-phenyl-1,2,3-triazoline, 10480-35-0; 1-(4-bromophenyl)-5-(2-pyridyl)-1,2,3-triazoline, 17843-17-3; 1-(3,4-difluorophenyl)-5-(2-pyridyl)-1,2,3-triazoline, 110684-19-0; 1-(3,4-dichlorophenyl)-5-(4-pyridyl)-1,2,3-triazoline, 106878-43-7; 1-(4-methoxyphenyl)-5-(2-quinolyl)-1,2,3-triazoline, 129239-62-9; 1-(4-methoxyphenyl)-5-(2-chlorophenyl)-1,2,3-triazoline, 91283-09-9; 1-(3,4-dichlorophenyl)-5-(2-chlorophenyl)-1,2,3-triazoline, 14717-17-0; 1-phenyl-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 14632-41-8; 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 91283-12-4; 1-(3-chlorophenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 14632-43-0; 1-(4-fluorophenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 128229-07-2; 1-(4-bromophenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 14632-44-1; 1-(4-(trifluoromethyl)phenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 128229-08-3; 1-(3-(trifluoromethyl)phenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 91283-11-3; 1-phenyl-5-(2,6-dichlorophenyl)-1,2,3-triazoline, 91283-13-5; 1-(4-chlorophenyl)-5-(2,6-dichlorophenyl)-1,2,3-triazoline, 128229-09-4; 1-(3-chlorophenyl)-5-(2,6-dichlorophenyl)-1,2,3-triazoline, 91283-14-6; 1-(4-bromophenyl)-5-(2,6-dichlorophenyl)-1,2,3-triazoline, 84817-34-5; 1-(4-(trifluoromethyl)phenyl)-5-(2,6-dichlorophenyl)-1,2,3-triazoline, 129239-63-0; 1-(3-(trifluoromethyl)phenyl)-5-(2,6-dichlorophenyl)-1,2,3-triazoline, 129239-64-1; 1-(3,4-dichlorophenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline, 14632-48-5; 1-(4-chlorophenyl)-5-(2-nitrophenyl)-1,2,3-triazoline, 129239-65-2; 1-(3,4-dichlorophenyl)-5-(2-nitrophenyl)-1,2,3-triazoline, 14717-16-9; 1-(3-(trifluoromethyl)phenyl)-5-(2-nitrophenyl)-1,2,3-triazoline, 129239-66-3.

Synthesis of Spiroketals: A General Approach

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A general procedure for the synthesis of functionalized spiroketals from lactones is described. Addition of the lithium acetylide of cis-1-methoxy-1-buten-3-yne to lactones followed by a hydration of the acetylene, hydrolysis of the enol ether and cyclization gives excellent yields of spiroketals containing a useful enone functionality.

The presence of highly substituted and functionalized spiroketals in many biologically significant natural products has stimulated a great deal of synthetic work directed toward the synthesis of these systems.[2] These include complex molecules such as calcimycin (A-23187),[3] okadaic acid,[4] monensin,[5] aplysiatoxin,[6] phyllanthocin,[7] and the

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